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Treacher Collins Syndrome: Phenotypic Variability in a Family Including an Infant With Arhinia and Uveal Colobomas

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We report extreme expression of Treacher Collins syndrome in an infant with arhinia, anotia, absent zygomatic bones, hypoplastic mandibular rami, and bilateral coloboma of iris, choroid plexus, and optic nerves. The Treacher Collins phenotype was mildly expressed in the mother and moderately in the sister. The father had no signs and was not ruled out as the father by DNA fingerprinting, thus making homozygosity by descent in the severely affected son very unlikely.

KEY WORDS: Treacher Collins syndrome, arhinia, anotia, uveal coloboma

INTRODUCTION

The findings in the Treacher Collins syndrome (TCS) were first described in the Western medical literature in 1889 [Berry, 1889]. Since then, many cases have been documented and a wide spectrum of expression noted among affected individuals even within the same family [Franceschetti and Klein, 1940; Franceschetti et al., 1949; Rogers, 1964; Marsh et al., 1986; Kolar et al., 1987; Peterson-Falzone and Figueroa, 1989; Kreiborg and Dahl, 1993]. We were unable to find another reported case with the phenotypic severity of this child.

CLINICAL REPORT

A 22-year-old woman was the first member of her family to have mild Treacher Collins syndrome. The diagnosis was made only after the birth of her first daughter who has a slightly more severe form of the syndrome (Fig. 1). Amniocentesis was performed during her next pregnancy at 16 weeks and DNA linkage analysis confirmed that the fetus most likely had the Treacher Collins gene. Furthermore, ultrasonographic examinations indicated that the fetus had very severe craniofacial anomalies consistent with this syndrome (Fig. 2). The mother decided to continue the pregnancy. The child was born normally at 37 weeks; respiratory distress required urgent intubation and subsequent tracheostomy. A gastrostomy tube was placed to facilitate feeding.

The reasons for these life-threatening problems were immediately apparent at birth (Fig. 3). The infant had severe Treacher Collins syndrome with anotia, absent zygomas and a markedly hypoplastic mandible. Arhinia was the most remarkable craniofacial abnormality. There was a small cutaneous dimple in the region where the nose should have been. His eyes were proptotic due to shallow, hypoplastic orbits. Corneal exposure was a chronic problem from birth. The eyelids had the characteristic downward slant and there was a small coloboma of the right upper lid. He had large-angle exotropia. The anterior segments manifested effects of corneal exposure, iris colobomas and transiently increased intraocular pressure. Ocular examination after dilatation showed bilateral choroidal and optic nerve colobomas. At age 5 months, a preferential-looking test disclosed vision of 20/670 OS and indeterminate acuity OD.

Fig. 1. The mother is mildly affected; however, her first child (a daughter) has moderately severe Treacher Collins syndrome.

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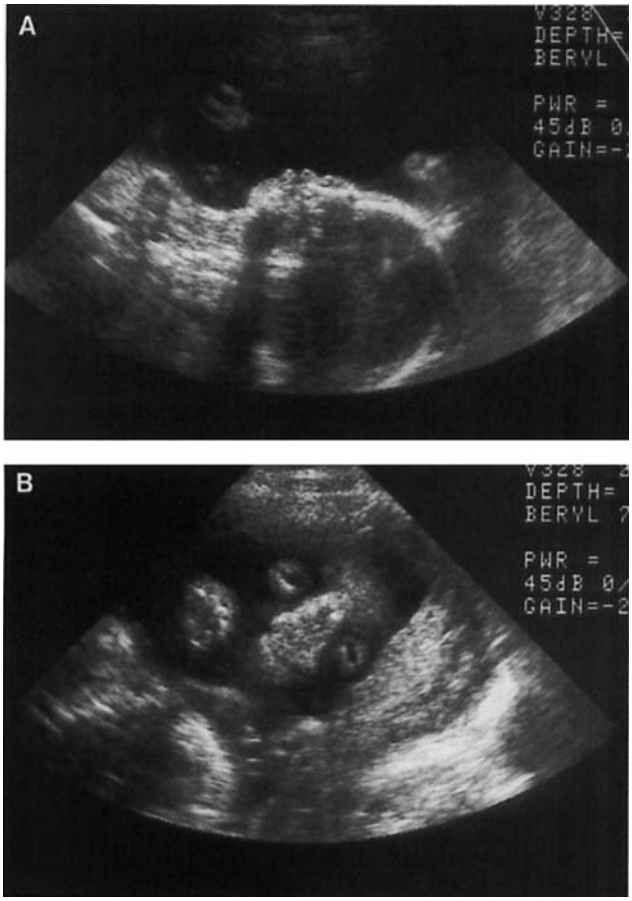

Fig. 2. Ultrasonography of the severely affected fetus in the second trimester. **A:** Sagittal (profile) view of fetus shows virtually complete absence of nose and micrognathia. **B:** Note typical slanted eyelids on coronal view of fetus.

Both mandibular condyles were palpated, yet they did not articulate with the temporal bones. The palate was very narrow and small. There was a curious indentation of the right alveolar ridge. No cleft of the palate was evident; indeed, there was no nasal cavity into which clefting could occur. Other abnormalities were microphallus and small scrotum. Hands, feet and other physical findings were normal. The cranial sutures were open.

The skeletal abnormalities were documented at 2 days after birth by CT scan and 3-dimensional reformation (Fig. 4). Absence of the zygomata was confirmed as was the floating mandible. Both maxillae and ethmoids were small. The nasal cavity was virtually absent. The cribriform plates were below the orbital floors and the frontal lobes extended between the eyes. There was only 1–2 mm of skeletal tissue between the cribriform plates and the palate. Large herniations of vitreous humor (choroidal colobomas) were present bilaterally, effacing each retina (Fig. 5). Computed tomography and ultrasonographic studies of the brain indicated that the corpus callosum was hypoplastic and also showed minor intraventricular hemorrhages.

Results of biochemical, endocrine, hematological and chromosome studies were normal apart from confirming linkage to the Treacher Collins locus at 5q33. Genetic fingerprinting did not exclude this child as having the same father as the mildly affected older sister. The father had no signs of Treacher Collins syndrome, thus ruling out the possibility of inherited homozygosity in his severely affected son.

DISCUSSION

Ocular adnexal abnormalities are principal components of Treacher Collins syndrome, as emphasized by Franceschetti et al. [1949]. Palpebral fissure obliquity

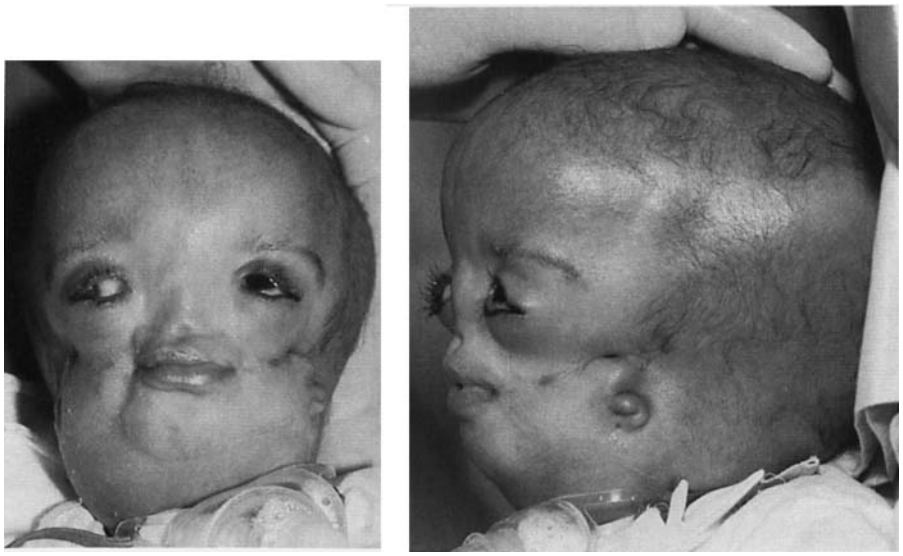

Fig. 3. Frontal (**left**) and lateral (**right**) photographs of the severely affected son shortly after birth and after tracheostomy. Note absence of nose and ears, ocular proptosis, iris colobomas, and mandibular condyles protruding beneath skin.

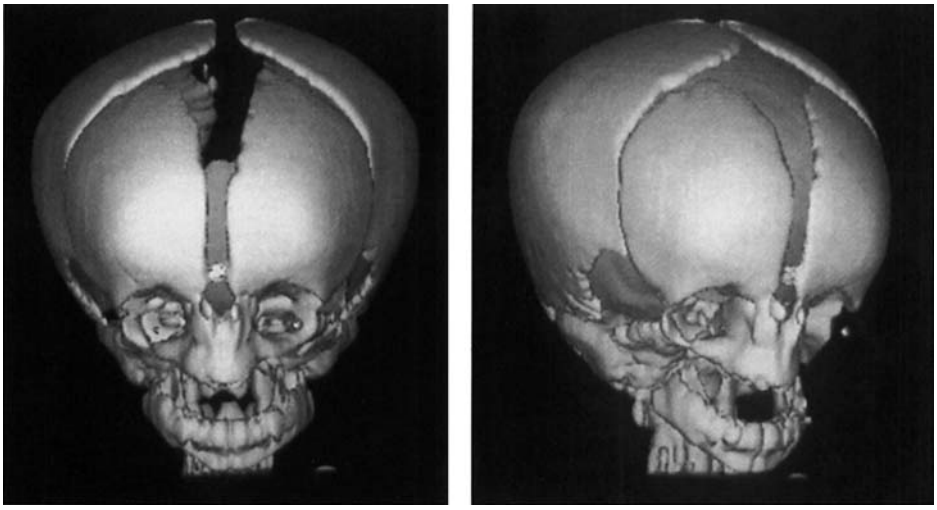

Fig. 4. Three-dimensional, frontal (**left**) and oblique (**right**) CT images obtained at age 3 days document skeletal abnormalities. Note absent nasal passages, zygomas, and mandibular rami.

and lower eyelid colobomas were noted in the first two cases described by Berry [1889]. The palpebral slant results from hypoplasia of the zygoma and is associated with "tear drop" shaped orbits and malar clefting into the sphenomaxillary fissure. Absence of the lateral canthal tendon has been demonstrated at operation [Bachelor and Kaplan, 1981] and in 9 of 9 patients on physical examination [Wang et al., 1990].

Colobomas of the lateral lower eyelid occur in 75% of cases [Geeraets, 1976]. In some affected individuals, there are partial defects in either the upper or lower eyelids due to hypoplasia of the tarsal plates and orbicularis muscle (pseudocolobomas).

Eyelashes are usually absent or sparse medially [Mann, 1943; Franceschetti and Klein, 1949; Hurwitz, 1954; Rogers, 1964]. In such cases there is a deficiency of the underlying tarsus and Meibomian glands. The lower lacrimal punctum and canaliculus may be absent, particularly in more severe cases [Hurwitz, 1954; Wille-Jorgensen, 1962; Prasad et al., 1984; Bartley, 1990]. Less commonly seen adnexal anomalies are blepharoptosis [Wille-Jorgensen, 1962], distichiasis [Bachelor and Kaplan, 1981; Hurwitz, 1954], ectropion, entropion and trichiasis [Franceschetti and Klein, 1949].

In most cases there is no intraocular pathology. Microphthalmos, ectopia of the pupil, and cataract are reported infrequently [Franceschetti and Klein, 1949; Hurwitz, 1954; Wille-Jorgensen, 1962; Roy, 1985; Fries and Katowitz, 1990]. Ectopic pupil probably is the result of coloboma of the iris. Uveal colobomas, as seen in this child, are very rare in Treacher Collins syndrome [Geeraets, 1976; Roy, 1985; Fries and Katowitz, 1990; Diamond et al., 1990].

Complete absence of the nose (arhinia) is rare [Nishimura, 1993]. We found one equivocal example of Treacher Collins syndrome with arhinia in the literature [Berndorfer, 1962]. However, this patient did not have the distinctive ocular and mandibular findings of the syndrome, as did our patient. The infant died at age 6 months due to acute respiratory obstruction but was thriving prior to this event.

Does this infant have an extreme form of Treacher Collins syndrome or a coincidental combination of Treacher Collins syndrome with some other condition? Characteristic physical findings in the mother and sister suggest that this child has Treacher Collins syndrome. Furthermore, the linkage study strongly supported that mother and child had the same mutation.

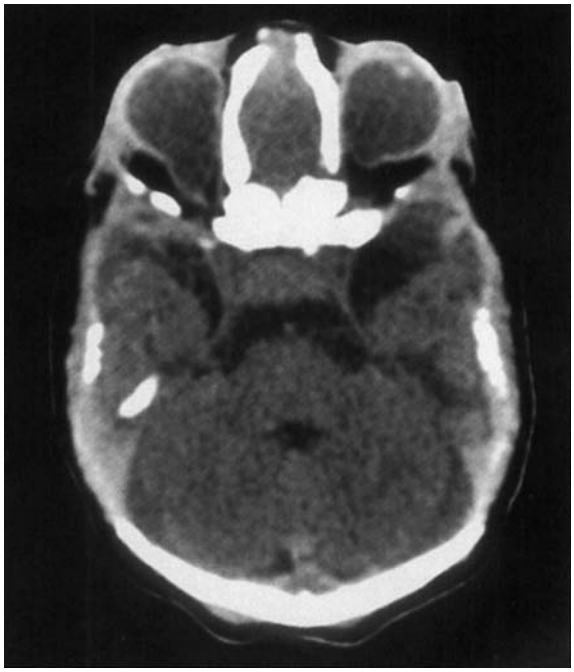

Fig. 5. Axial computed tomogram, at level of eyes, demonstrates bilateral uveal colobomas and severe proptosis.

Irrefutable confirmation would require identification of the precise mutation in this child. This disorder has been mapped to 5q33 but the responsible gene has not been identified or sequenced [Dixon et al., 1993; Jabs et al., 1993]. Homozygosity is another possibility but since the father has no signs of TCS this would be a remote occurrence, requiring a coincidental mutation of the normal allele.

Another conceivable explanation is that a teratogen interacted with the genetic mutation to produce the abnormal phenotype. We were unable to ascertain a history of drug or substance (ab)use from the mother; however, the social circumstances suggested this possibility. Alcohol, in particular, is associated with midface and nasal hypoplasia as well as ocular anomalies [Gorlin et al., 1990].

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